INSTITUTO DE BIOLOGÍA FUNCIONAL Y GENÓMICA

Programa de Seminarios Externos **Viernes, 26 de Abril de 2019**

Regulation of TORC1 by Amino Acids: a Central Role for Rag GTPases Within the EGO Complex

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Abstract: The eukaryotic target of rapamycin complex 1 (TORC1) couples nutrient, energy, and hormonal signals with cell growth, division, and metabolism, and aberrant TORC1 signaling contributes to the progression of human diseases such as cancer and diabetes. Amino acids are important and primeval cues that stimulate TORC1 to promote anabolic processes (such as ribosome biogenesis and protein translation initiation) and inhibit catabolic processes (such as macroautophagy) via the conserved Rag family GTPases. The latter assemble into heterodimeric complexes consisting of Gtr1 and Gtr2 in yeast, or RagA or RagB and RagC or RagD in mammalian cells. These heterodimers are integral to larger complexes coined EGO (exit from rapamycin-induced growth arrest) complex (EGOC) in yeast or Rag-Ragulator complex in mammalian cells, which are predominantly tethered to vacuolar/lysosomal membranes. Because Rag GTPase heterodimers stimulate TORC1 when they contain GTP-loaded RagA/B/Gtr1 and GDP-loaded RagC/D/Gtr2, GTPase activating proteins (GAPs) acting on Gtr1/RagA/B, such as the orthologous yeast SEACIT or mammalian GATOR1 complexes inhibit, while the ones acting on Gtr2/RagC/D, such as the yeast Lst4-Lst7 or the orthologous mammalian FNIP1/2-Folliculin (FLCN) complexes, activate TORC1. The amino-acid sensitive events upstream of GATOR1 that inhibit TORC1 signaling include the cytosolic leucine and arginine sensors Sestrin2 and CASTOR1, respectively. Both sensors stimulate GATOR1 under amino acid deprivation via a poorly understood mechanism involving their binding to the conserved GATOR1-interacting GATOR2 complex coined SEACAT in yeast. How amino acids activate TORC1 through the Lst4-Lst7/FNIP1/2-FLCN GAP complexes is currently not known. In this context, our current research is focused on deciphering the amino-acid sensitive events upstream of the Rag GTPase regulators in yeast, which likely involve both vacuolar and cytoplasmic amino acid sensors. Due to the evolutionary conservation of the EGOC and its regulators, our studies in yeast are expected to contribute to the understanding of the molecular mechanisms leading to diseases that are associated with hyperactive mammalian TORC1.

Fecha: 26 de Abril de 2019
Hora: 12:30
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